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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,724	12/08/2003	Antonius Arnoldus Christiaan Jacobs	I 1999.452 US C1	5481

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,724	JACOBS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/11/05 has been acknowledged.
Claims 1-5 are canceled.
Claims 6-11 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Double Patenting

Claims 6-11 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,682,745 for the same reasons of record as set forth in the office action mailed on 01/11/05.

Claims 6-8 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,120,775 (ref. of record), for the same reasons of record as set forth in the office action mailed on 01/11/05.

Response to Arguments

Regarding the double patenting issues above, the applicant requested the rejection be held in abeyance until allowable subject matter is identified, therefore the rejection is maintained.

Claim Rejections - 35 USC § 112

Claims 6-11 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 01/11/05.

The scope of the instant invention as claimed encompasses a method of administering a live attenuated bacterial vaccine (any bacteria) to a mammal by injecting the vaccine into submucosal layer of a mammal. The scope of invention as claimed further encompasses a method for reducing the amount of adverse reaction in a mammal at injection site of live attenuated bacterial vaccine (any bacteria) by administering the vaccine submucosally. The scope of invention as claimed encompasses the use of any and all live attenuated bacteria. At best the instant specification only discloses the use of *Streptococcus equi* attenuated strains (TW 928 and TW928/sls), which are deletion mutant vaccine strains (spec. page 7, example-1). Besides TW 928 (*Streptococcus equi)* the instant specification fails to disclose any live attenuated vaccine obtained from any other bacterial strain. Especially the specification fails to disclose a live attenuated vaccine obtained from *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis* explicitly or implicitly as putatively considered by the applicant.

The state of the art regarding attenuated bacterial vaccine was such that a rational approach to design a live attenuated bacterial vaccine involves genetic

modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. (Curtiss R. J. Clin. Invest. 110(8):1061-1066; 2002, ref of record). In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. For example, inactivation of PhoP/phoq regulatory system in S. typhi results in strains, which are suitably attenuated for use as vaccines (Tiball et al Vaccine 19:4175-4184, 20001, *ref of record*, see page 4177 sec 3.1). Even though instant specification discloses only *Streptococcus equi* based attenuated strains (TW 928 and TW928/sls) the disclosure is considered insufficient, since the specification fails to disclose how to attenuate of any other species of bacteria that can be used as a vaccine without any adverse reaction. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

Furthermore, the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case claims to live attenuated bacteria has been defined only by a statement of bacterial growth and proliferation (live attenuated) which conveyed no distinguishing information about the identity of various live attenuated bacterial species (as claimed), such as genetic modification or antigenic characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only

one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Response to Arguments

Applicant's arguments filed on pages 7-11 regarding written description issues, have been fully considered but they are not persuasive. The applicant argues that the subject matter of the claim need not to be described literally in order for disclosure to satisfy the written description requirement. The applicant argues that the specificaiton has shown the represntative number of live attenuated bacterial strains which represent the applicant had possession of the claimed invention. The applicant argues that the claim are drawn to a method of vaccinating mammal and not acctual vaccines of live attenuated bacterial strains.

However, applicant's argumetns are found not persuasive because the method as claimed requires a product that has not been fully described the instant specificaiton. Besides the TW 928 (*Streptococcus equi)* the instant specification fails to disclose any other live attenuated vaccine obtained from a bacterial strain selected from *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis*. In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described. Besides TW 928 (*Streptococcus equi)* the specification does not describe any other live attenuated bacteria as listed above. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In instant case live attenuated *Streptococcus equi does not represent a common core structure of the genus claimed sine bacterial strains as claimed represent species that are distinct.* Since the specification fails to disclose any other live attenuated bacteria or a

common relevant identifying characteristics, it is not possible to envision the claimed method in view of product that need to be administered. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). As stated above the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the attenuation is an inherent property of the bacterial vaccine and is not dependent on fully functional host defenses and immune response capabilities. The attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. Even though instant specification discloses only *Streptococcus equi* based attenuated strains (TW 928 and TW928/sls) the disclosure is considered insufficient, since the specification fails to disclose how to attenuate of any other species of bacteria that can be used as a vaccine without any adverse reaction. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Claims 6-11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting a mammal against *Streptococcus equi* infection by administering a live attenuated *Streptococcus equi* strain (TW980), does not reasonably provide enablement for a method for protecting a mammal against all bacterial infection by administering any and all live attenuated bacterial strains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 01/11/05.

Nature of invention

The instant invention is drawn to live attenuated bacterial vaccine.

Breadth of Claims and Guidance Provided in the Specification

The scope of the instant invention as claimed encompasses a method of administering a live attenuated bacterial vaccine (any bacteria) to a mammal by injecting the vaccine into submucosal layer of a mammal. The scope of invention as claimed further encompasses a method for reducing the amount of adverse reaction in a mammal at injection site of live attenuated bacterial vaccine (any bacteria) by administering the vaccine submucosally. The scope of invention as claimed encompasses the use of any and all live attenuated bacteria. At best the instant specification only discloses the use of *Streptococcus equi* attenuated strains (TW 928 and TW928/sls), which are deletion mutant vaccine strains (spec. page 7, example-1). Besides TW 928 (*Streptococcus equi)* the instant specification fails to disclose any live attenuated vaccine obtained from any other bacterial strain. Especially the specification fails to disclose a live attenuated vaccine obtained from *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis* explicitly or implicitly as putatively claimed herein.

State of art and predictability

The state of attenuated bacterial vaccine art teaches was such that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. (Curtiss R. J. Clin. Invest.

110(8):1061-1066, 2002, ref. of record). In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. For example, inactivation of PhoP/phoq regularoty system in S. typhi results in strains, which are suitably attenuated for use as vaccines (Tiball et al Vaccine 19:4175-4184, 20001, *ref of record*, see page 4177 sec 3.1). Furthermore, the development of live attenuated bacterial vaccine has not been always predictable. For example, development of a live attenuated *Shigella* vaccine that is sufficiently attenuated to be non-reactive yet adequately invasive to be highly immunogenic took 30 years in making, since it required substantial understanding of molecular genetic basis of virulence of *Shingella* (Curtiss page 1063, col.2). Although, the instant specification discloses *Streptococcus equi* based attenuated bacterial strains (TW 928 and TW928/sls), it fails to provide any guidance regarding the attenuation of any other species of bacteria. For example, the specification fails to provide any guidance regarding how to make a live attenuated bacterium selected from the above-mentioned species (see claims 7 and 11). The specification fails to disclose what are the bacterial regulatory systems in these bacteria, mutation of which would result in the making of a live attenuated bacterial strain that would provide protect a mammal against any specific bacterial infection. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case to practice the invention, as claimed one would require a live attenuated vaccine on hand.

However the specification fails to provide any guidance regarding how make a live attenuated vaccine for all bacterial strains (other than *Streptococcus equi* attenuated strains TW928).

In addition, making any and all types of live attenuated bacterial vaccines and protecting a mammal against any and all type of bacterial infection using the live attenuated bacterial vaccines (wherein the attenuation of a specific bacterial genetic regulatory system has not been disclosed) are not considered routine in the art and without sufficient guidance to a specific bacterial strain experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The amount of undue experimentation required would include characterization of any and all bacterial strains (as claimed) to find out which regulatory systems could be genetically manipulated so that the attenuation renders the bacterium non-virulent while maintaining the stability of protective antigen expression that provides immune protection. In addition the undue experimentation required would further include the testing of all attenuated bacterial species in any and all mammals to evaluate of the efficacy of the live attenuated bacterial vaccine made.

Response to Arguments

Applicant's arguments filed on pages 9-11 regarding enablement issues have been fully considered but they are not persuasive. The applicant argues that the invention as claimed is drawn to a method of administering a bacterial vaccine and not for a method of protecting a mammal from bacterial infection. The applicant argues that the method of administering by injection of any bacterial vaccine into submucosal tissue is fully enabled. The applicant argues that the as long as the specification discloses at least one method for making and using the claimed invention it bears a reasonable corelation to the entire scope of the claim. The applicant argues that the a skilled artisan would not suffer an unde burden to practice the present invention. The applicant concluded that when a viable live attenuated vaccine is at hand administratiion by injecntion is clealry enabled.

However, applicant's argumetns are found not persuasive because the method as claimed requires a product that has not been fully described the instant specificaiton. Even though the scope of invention as claimed encompasses a submucosal injection it requires the use of various attenuated bacterial strains like *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli; Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis*, which has not been disclosed in the instant specification. Therefore it would requrie an undue amout of exprementation to administer a live attenuated bactria or a live attenuated bactrial vaccine selected from the above-mentioned bacterial strains. Furthermore invention as claimed is not merely administration of a bacterial strain because the only disclosed utilty of the calimed method is protection of mammal from a bacterial infection. MPEP clearly states that office is to give claims their broadest reasonable interpretation in light of the supporting disclosure. See In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) and MPEP 2100. The earlier office action clearly provided the evidence that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. The attenuation of a bacterium requires the knowledge and modification of specific bacterial genes that render the bacterial strain non-virulent.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is*

not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case to practice the invention, as claimed one would require a live attenuated vaccine on hand. However the specification fails to provide any guidance regarding how make a live attenuated vaccine for all bacterial strains (other than *Streptococcus equi* attenuated strains TW928).

In addition, the live attenuated bacterial vaccines for claimed bacterial strains are not readily available in the art and without sufficient guidance to a specific bacterial strain experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The amount of undue experimentation required would include characterization of bacterial strains (as claimed) to find out which regulatory systems could be genetically manipulated so that the attenuation renders the bacterium non-virulent while maintaining the stability of protective antigen expression that provides immune protection. In addition the undue experimentation required would further include the testing of all attenuated bacterial species in any and all mammals to evaluate of the efficacy of the live attenuated bacterial vaccine made.

Conclusion

No claims are allowed.

Note: An non-final office action is only issued to correct the typographical error found in double patenting rejection of claims 6-11 over claims 1-4 of U.S. Patent No. 6,682,745 for the same reasons of record as set forth in the office action mailed on 01/11/05.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1633